LungGO COPDGene Exomes Preliminary Analysis

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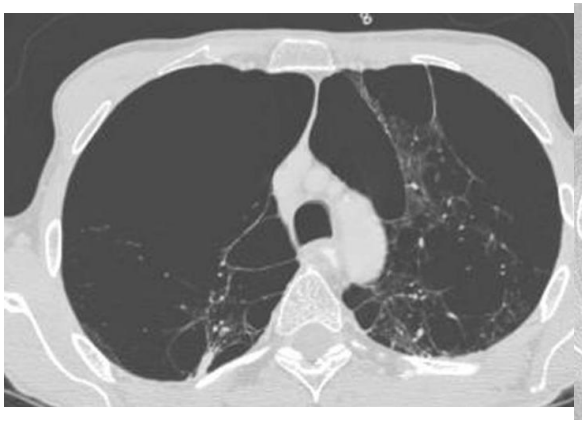
COPDGene® COPD Genetic Epidemiology (COPD Smoking)

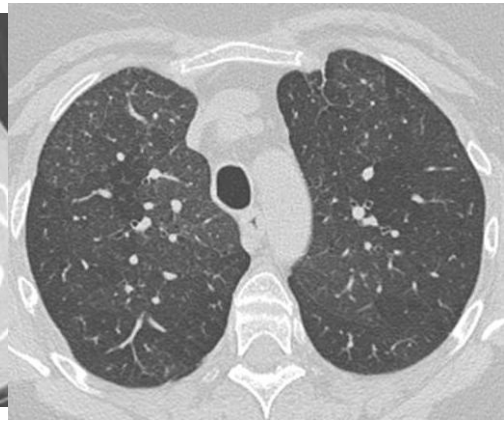
- Rising to 3rd as a cause of death in the US
- Rare coding variants are important in COPD
  - Alpha-1 antitrypsin deficiency - ~1% cases
  - Glu342Lys in *SERPINA1*
- Exome sequencing
  - Extremes of susceptibility to similar degrees of cigarette smoke
  - Use lung function *and* emphysema

	Male	Age	Pack-years	FEV_1 %	Emphysema
Cases (n=205*)	51%	57.3	50.2	30.1	30.0
Controls (n=196*)	44%	70.4	50.0	100.0	1.9

*127 subjects sequenced through the COPD Foundation with support from Pfizer



Age 42, FEV_1 38%



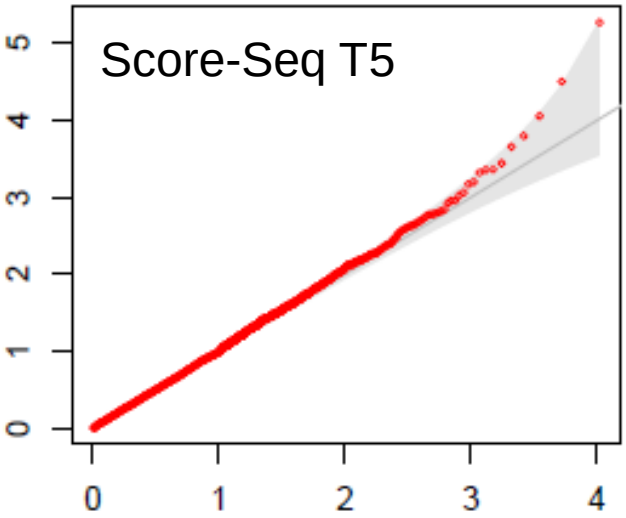
Age 47, FEV_1 20%

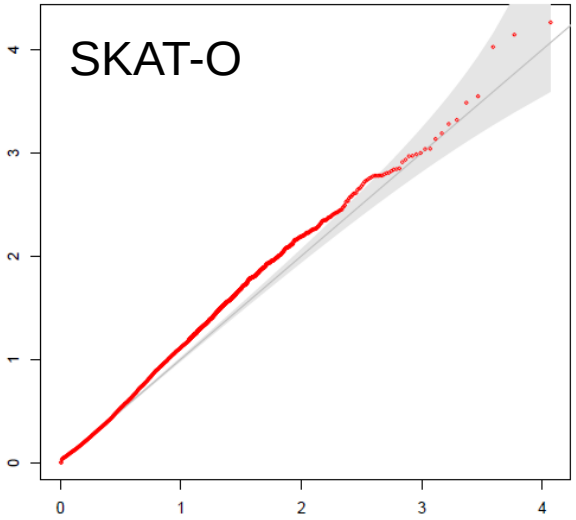
QC and Analytic Methods

- Quality control
  - Subjects: gender, race / PC outlier, GWAS concordance, duplicates
  - Variants: GATK ESP standard filter; missingness, depth, hwe
  - SNPs annotated using SnpEff (+PPH2, SIFT, SeattleSeq)
- Association analysis
  - Requirements
    - Inclusion of covariates (principal components)
    - Deal with asymptotic assumptions (e.g. permutation)
  - Primary analysis (current)
    - T5 for deleterious (eg NS, STOP) using resampling as implemented in Score-seq
  - Alternatives
    - SKAT-O
    - Score-Seq: Madsen-Browning-like (Fp), Variable threshold (VT)
    - Others

Lin / Tang AJHG 2011; Lee-S et al 2012

Preliminary Results





Gene	T5	SKAT-O
SHROOM3	7.6×10^{-6}	5.4×10^{-5}
SUN2	3.8×10^{-5}	9.4×10^{-5}
DMWD	8.7×10^{-5}	7.2×10^{-5}
KIF14	2.1×10^{-4}	3.2×10^{-4}
PCDHA6	4.3×10^{-4}	7.3×10^{-4}

- Additional QC TBD
  - GWAS concordance, resolve duplicate issues
  - SVA (vs VQSR) variant calls
  - Indels

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